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Multitargeted drugs: the end of the 'one-target-one-disease' philosophy?

In a recent issue of *Drug Discovery Today*, Morphy *et al.* [1] discuss the opportunities and advantages associated with the design of ligands that act on two (or more) specific targets in an article entitled 'From magic bullets to designed multiple ligands'.

Several highly specific drugs that have only one target have clearly proven the usefulness of monotarget medicine. Examples of such drugs include the phosphodiesterase 5 inhibitors (e.g. sildenafil), the α_{1a}-adrenoceptor antagonist drugs (e.g. tamsulosin), the selective cyclooxygenase-2 inhibitors (e.g. celecoxib) and the kinase-specific anticancer drugs (e.g. imatinib). However, clinicians are becoming increasingly convinced that modulating a multiplicity of targets can be an asset in the treatment of a range of disorders. An extreme example of a multitarget drug is clozapine, which exhibits nanomolar affinities for more than a dozen different receptors.

In some instances, multitargeting can be achieved by simply combining several drugs that independently have only one specific target. This approach is used in AIDS tritherapy, where a single-dose of two reverse transcriptase inhibitors and one protease inhibitor is administered, in the treatment of infection, where the β-lactamase inhibitor clavulanic acid is used in conjunction with amoxicillin, and in the treatment of Parkinson's disease, where L-4-dihydroxyphenylalanine (DOPA) is concomitantly administered with DOPA-decarboxylase and catechol-*O*-methyltransferase inhibitors. The risk with combination therapies is that the use of multiple drugs introduces problems with pharmacokinetics, toxicity and patient compliance. To circumvent these difficulties, and after an analysis of the literature, Morphy *et al.* [1] propose that 'designed multiple' (DM) ligands (predominantly dual ligands) are prepared according to two approaches – pharmacophore combination and oriented screening.

The 'combination of pharmacophores' strategy comprises the combination of crucial structural elements (i.e. those functionalities that are required for biological activity) from two molecules to produce one molecule. The two combined elements yield a 'non-identical twin drug', which can result either from two active molecules that are linked by an appropriate spacer or from the overlap of a common structural feature of the two molecules. The basis of this approach is well codified and there are numerous examples in the literature [2–5]. Like many others, the authors use the term pharmacophores to define functional or structural elements that possess biological activity. However, this does not correspond to the official definition [6]: 'A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response.' A pharmacophore does not represent a real molecule or an actual association of functional groups, but is a purely abstract concept that encompasses the common molecular interactions of a group of compounds with their target structure. Pharmacophores are not 'pieces of molecules', and for this reason a truly rational computer-generation of DM ligands should not be based on the interactions of structural elements, but rather the comparison and association of true pharmacophores.

The second approach (screening approach) to DM ligands is based on the screening of large libraries for the two relevant bioassays. The substantial screening of a large number of compounds, which therefore have a significant number of targets, makes the design of *de novo* molecules possessing affinities of similar potency for two different targets feasible. Once the DM ligand has been identified, the 'usual' medicinal chemistry work-up has to be done to render the molecule bioavailable, to confer a satisfactory pharmacokinetic profile and to achieve some chemical formulation procedures. The risk in performing these manipulations is that the balanced potency of the two profiles could be disrupted.

An interesting alternative to the production of dual-acting drugs starts from a multiple-target drug, which is then modified to reduce, or delete, all unwanted affinities. Hanano *et al.* [7] recently reported the preparation of a selective dual-acting cytokine regulator with tumor necrosis factor-α (TNF-α)

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suppressing and interleukin-10 (IL-10) augmenting activities. The dual-acting molecule was developed from an initial CNS lead that had nanomolar affinities not only for TNF-α and IL-10 targets, but also for dopamine-2, 5-hydroxytryptamine (HT)-1A, 5-HT_2 and 5-HT_1 receptor preparations.

In conclusion, the preparation of dual- or multiple-ligands on an almost rational basis is now conceivable and it can be expected that many of these molecules will yield drugs of superior clinical value compared with monotarget formulations.

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Trends in the use of ultrasound-mediated transdermal drug delivery

The skin is an appealing route for the delivery of drugs because it offers the efficacy of injection with an ease of use that is comparable with oral administration. However, transdermal drug delivery is limited to those drugs that comprise small molecules (<500 Da). Consequently, emerging techniques that have the potential to increase the number of drugs that could be administered by this route are the focus of extensive research. There are various enhancers, for example, chemicals and electrical current (iontophoresis and electroporation), that are currently being investigated as methods for improving the transdermal delivery of drugs. An additional enhancer that has received considerable attention is the use of ultrasound (sonophoresis), a topic that was addressed by Lavon and Kost [1] in a recent issue of *Drug Discovery Today*.

Since the initial results reported by Fellinger [2], the efficacy of ultrasound has been widely demonstrated with small and large molecules. Today, the delivery of large molecules (e.g. insulin) at low frequency ultrasound (<100 kHz) has encouraged a greater interest in increasing skin permeability [3–5]. Moreover, the use of ultrasound has been extended to monitoring glucose levels in blood [6], which demonstrates that skin permeabilization via the application of ultrasound could enable the delivery of molecules to the body and facilitate the withdrawal of molecules from the body. The interest in ultrasound-mediated molecule delivery is thus based on two factors: (i) the capacity to enhance the efficacy of existing transdermal formulations (e.g. anesthetics and non-steroidal anti-inflammatory drugs) by improving the topical action of the drug; and (ii) the potential of sonophoresis for the improvement of patient compliance in therapeutic domains such as diabetes and psychiatry and also in the delivery of vaccines. With an increasing number of biomolecules emerging from biotechnology, the choice of the best route of administration is becoming crucial, and the transdermal mode appears to be an excellent candidate in some cases (e.g. treatment of psoriasis).

One of the key issues for the success of sonophoresis technology remains the development of low cost ultrasound devices that enable efficient transdermal drug delivery. Although low-frequency sonophoresis has been extensively studied in the past ten years, there are no low-frequency sonophoresis devices commercially available today. The principal difficulty lies in the development of a miniaturized low-frequency ultrasound device that is powerful enough to create pathways within the skin. There are two prototypes of low-frequency sonophoresis devices for which preliminary human pilot trials have already been conducted. An ultrasonic skin-permeation instrument [SonoPrep® (Sontra Medical; http://www.sontra.com)] was used in a Phase I clinical study performed in patients with diabetes [7]. In another study, rapid cutaneous anesthesia (5 min) was achieved after pretreatment with the SonoPrep® (10 s) followed by application of EMLA® cream (AstraZeneca; http://www.astra.com) [8]. Transdermal insulin delivery has been achieved in a preliminary human pilot trial using a device developed by Encapsulation Systems (EX1–4; http://www.encsys.com) that comprises a four-element transducer array containing a special cymbal transducer.

Research using sonophoresis and other chemical or physical enhancers has significantly advanced knowledge on the structure and function of the skin. However, the primary role of the skin is to protect the body against the environment and, therefore, one of the questions that remains concerns the long-term biological effects of multiple ultrasound applications at the same site of the body in terms of skin physiology. This emphasizes the need to perform further skin tolerance studies to